Table 79. Weight Gain and Blood Pressure Effects for Patients with Peripheral Edema: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

	Placebo	Celecoxib 50-400 mg BID	Naproxen 500 mg BID
	N=1136	N=3380	N=1099
Incidence of peripheral edema (% of patients)	1.1%	2.5%*	2.2%*
Percent of patients with peripheral edema and a weight gain ≥1 kg	0.5%	0.7%	0.8%
Mean weight change in patients with peripheral edema (kg; mean ± SE)	0.43 ± 0.71	0.27 ± 0.34	0.64 ± 0.49
Mean weight change in patients without peripheral edema (kg; mean ± SE)	0.13 ± 0.15	0.26 ± 0.05	0.27 ± 0.08
Mean change in diastolic blood pressure in patients with peripheral edema (mmHg; mean ± SE)	-1.3 ± 4.2	-0.5 ±1.3	0.5 ± 1.5
Mean change in diastolic blood pressure in patients without peripheral edema (mmHg; mean ± SE)	-1.0 ± 0.3	-0.5 ±0.2	-0.4 ± 0.3

* Significantly different from placebo; $p<0.05$

6.3.10.3.2 Adverse Events Causing Withdrawal

Table 80 summarizes the incidence of withdrawals due to renal-related adverse events in the North American Controlled Arthritis Trials. The incidence of withdrawal due to edema or hypertension was low and no evidence for either dose-related or treatment-related effects was evident. Other reasons for withdrawal included the occurrence of increased creatinine in one patient treated with celecoxib 50 mg BID, one patient receiving celecoxib 200 mg BID, and one NSAID-treated patient. Two patients, one receiving placebo and the other celecoxib 200 mg BID, discontinued study participation due to renal calculus. Two patients receiving placebo discontinued treatment due to hematuria or abnormal renal function. Finally, one patient receiving celecoxib 400 mg BID withdrew as a result of uremia and hyperkalemia.

Table 80. Incidence of Renal-Related Adverse Events Causing Withdrawal: North American Controlled Arthritis Trials

Adverse Event	Placebo	Celecoxib					NSAID
		50 mg BID	100 mg BID	200 mg QD	200 mg BID	400 mg BID	
No. treated	1864	690	1779	453	1914	615	2098
Any renal event	0.2	0.1	0.2	0.0	0.4	0.5	0.2
Hypertension	0	0	<0.1	0	0.1	0	<0.1
Aggravated hypertension	0	0	0	0	0.2	0	0
Generalized edema	0	0	0	0	0	0.2	<0.1
Peripheral edema	<0.1	0	0	0	0	0.2	<0.1

Data are expressed as percent of patients

6.3.10.3.3 Serious Adverse Events

In the North American Controlled Arthritis Trials, there were 10 patients with serious adverse events related to renal function. Cardiac failure occurred in one placebo-treated patient and pyelonephritis occurred in a patient receiving ibuprofen. In celecoxib-treated patients, the following serious adverse events occurred: hypertension or aggravated hypertension (three patients), cardiac failure (two patients), renal calculus (two patients), and quinine-induced uremia (one patient).

Thirteen renal-related serious adverse events occurred in the North American Long-term Open Label Arthritis Study resulting in an incidence of 5 events per 1000 patient-years of exposure. This compares with an incidence of 7 events per 1000 patient-years for serious renal-related adverse events in patients receiving celecoxib in the controlled arthritis trials. In the North American Long-term Open Label Arthritis Study, there was one case of acute renal failure associated with obstructive uropathy, three cases of cardiac failure, two cases of renal calculus, one patient with aggravated hypertension, one occurrence of diuretic-induced hyponatremia, one case of hydronephrosis, two patients with pyelonephritis, one patient with renal colic and one patient with hypokalemia.

6.3.10.3.4 Clinical Laboratory Results

Table 81 displays incidence of clinical laboratory abnormalities related to renal function occurring in the North American 12-Week Placebo- and Active-Controlled Arthritis Trials (Studies 020, 021, 022, 023, and 054). Extreme changes in renal-related clinical laboratory results were infrequent and differences across the treatment groups were

generally not evident. Moderate abnormalities in renal-related laboratories were more common. The incidence of moderate changes in serum sodium, chloride and potassium were higher with celecoxib and naproxen than with placebo. Treatment-related effects were not observed between celecoxib and placebo for all other renal-related clinical laboratory parameters.

Table 81. Incidence of Clinical Laboratory Abnormalities Related to Renal Function: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

Parameter	Celecoxib 100 mg and 200 mg BID		Placebo		Naproxen 500 mg BID	
	No. of Patients(a)	%	No. of Patients(a)	%	No. of Patients(a)	%
BUN	2122		1042		1036	
>9.3 mmol/L		3.3		1.3		6.1
>14.3 mmol/L		0.1		0		0.1
Creatinine	2189		1080		1072	
> 176.8 µmol/L		0.1		0		0
> 265.2 µmol/L		0		0		0
Sodium	2060		1009		1004	
<135 mmol/L		6.3		4.3		7.4
<120 mmol/L		0		0		0
Potassium	2063		1037		1020	
>5.0 mmol/L		5.1		2.3		5.8
>6.0 mmol/L		0		0		0
Chloride	2101		1031		1025	
>110 mmol/L		8.6		4.9		8.3
>130 mmol/L		0		0		0
Calcium	2183		1079		1070	
<1.7 mmol/L or >15% decrease		0		0		0
<2.0 mmol/L		0.3		0		0.5
Phosphate	1868		920		900	
<0.97 mmol/L		20.1		17.2		30.8
<0.32 mmol/L		0		0		0
Uric Acid	2056		1003		978	
<148.7 µmol/L		0.8		0.5		0.7
<119 µmol/L		0.1		0.2		0.1
Urine pH	2135		1032		1040	
>8		0		0		0
>8.5		0		0		0.2
Urine Protein	2071		1006		1016	
Trace		2.6		2.6		3.8
1+ (300 mg/24/h)		1.2		1.3		0.6
Urine Glucose	2089		1017		1012	
Trace		0.9		0.9		0.5
1+ (1 g/24/h)		2.4		1.6		1.3
Urine RBC	2043		976		991	
>5/hpf		2.1		1.8		2.8
>10/hpf		4.2		3.7		4.3

a) No. of patients with normal values at Baseline

6.3.10.3.5 Effects on Blood Pressure

In the North American Placebo- and Active-Controlled 12-Week Arthritis Trials, mean blood pressure decreased slightly from Baseline to Final Visit in all treatment groups (Table 82). Although there were statistically significant differences between celecoxib 100 and 200 mg BID and placebo for change in systolic and diastolic blood pressure ($p<0.001$ and $p=0.017$, respectively), the differences were small and of no clinical significance. There was no pattern of increasing blood pressure with increasing celecoxib doses. Among patients in the North American Placebo- and Active-Controlled 12-Week Arthritis Trials, there was no statistically significant difference in the mean change in blood pressure from Baseline to Final Visit between celecoxib 400 mg BID and NSAIDs. There was a statistically significant difference between celecoxib 400 mg BID and placebo ($p=0.021$), but this difference was small (-0.5 mmHg compared to -2.1 mmHg) and not considered clinically meaningful.

Table 82. Analysis of Blood Pressure Between Celecoxib and Placebo or NSAID: North American Placebo- and Active-Controlled 12-Week Arthritis Trials

Laboratory Value	Celecoxib* (N=4410)	Placebo (N=2194)	p-value	Celecoxib* (N=4410)	NSAID (N=2150)	p-value
Mean Change from Baseline to Final Visit – mmHg						
Systolic BP	-0.5	-1.9	<0.001	-0.5	-0.9	-
Diastolic BP	-0.4	-1.0	0.017	-0.4	-0.5	-

*Column combines celecoxib 100 and 200 mg BID.

Blood pressure results from the North American Long-term Open Label Arthritis Study demonstrated that celecoxib did not markedly affect blood pressure with treatment up to 15 months (Table 83). The greatest mean change from baseline in blood pressure was reported at Week 2: -1.2/-0.6 mmHg.

Table 83. Change from Baseline in Blood Pressure: North American Long-term Open Label Arthritis Study

	Celecoxib*						
Laboratory Value	Week 2 (N=504)	Week 6 (N=523)	Week 12 (N=1873)	Month 6 (N=1420)	Month 12 (N=479)	Month 15 (N=112)	Final (N=3753)
Mean Change from Baseline – mmHg							
Systolic BP	-1.2	-0.0	-1.1	0.1	0.7	0.9	-0.6
Diastolic BP	-0.6	0.2	-0.4	-0.6	-0.4	0.1	-0.6

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6.3.10.3.6 Studies to Assess Renal Effect of Celecoxib

To evaluate the effects of celecoxib on renal function, three clinical pharmacology studies (Studies 010, 033 and 036) were conducted in selected groups of subjects and patients who have been identified at risk for adverse renal hemodynamic effects or excretory changes related to use of NSAIDs. A principal outcome measure in these studies was glomerular filtration rate (GFR, determined using Glofil®, sinistrine or inulin).

Renal Effects in Healthy Elderly Subjects: Study 010

In a single-center, in-patient, single-blind, randomized, crossover study, healthy elderly subjects (65 to 85 years of age) received either celecoxib 200 mg BID for five days followed by celecoxib 400 mg BID for the next five days, or they received naproxen 500 mg BID for 10 days. After taking one of these treatments and undergoing a seven-day washout period, subjects were crossed over to the other treatment regimen.

As depicted in Figure 30, GFR was unchanged from baseline (80.1±2.6 mL/min/1.73m^2) with celecoxib 200 mg BID on Day 1 and following escalation to 400 mg BID on Day 6. In contrast, GFR was reduced by 6% on Day 1 and 9% on Day 6 with naproxen 500 mg BID from a baseline value of 84.3 ± 2.9 mL/min/1.73m^2. A statistically significant reduction in GFR with naproxen 500 mg BID was detected on Day 6 when compared to the effect of celecoxib 400 mg BID. Five subjects exhibited 20% or greater reductions in GFR during naproxen 500 mg BID administration on either Day 1 or Day 6 as compared to Baseline. None of the subjects were observed to have 20% or greater reductions in GFR with either celecoxib 200 mg BID or celecoxib 400 mg BID.

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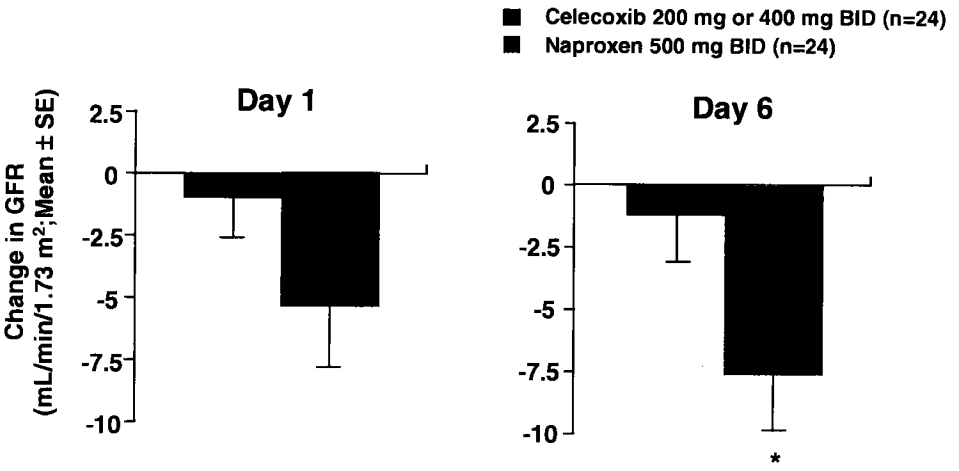
Figure 30. Glomerular Filtration Rate - Effect of Celecoxib vs Naproxen: Study 010



* Significantly different from naproxen; p <0.05.

Celecoxib and naproxen were associated with generally similar effects on urinary sodium excretion in terms of both the magnitude of the observed changes and the temporal pattern (Table 84). The significance of these observations is unclear since dietary sodium intake was not controlled in this study.

Table 84. Sodium Excretion Responses to Celecoxib in Healthy Elderly Subjects: Study 010

		Treatment Period Day (Mean Change ± SE from Baseline)								
Treatment	Base-line	1	2	3	4	5	6	7	8	9
Celecoxib	137 ± 10	-41 ± 10*	-29 ± 13*	-12 ± 10	-14 ± 9	-6 ± 11	-19 ±10	-26 ± 10*	-1 ± 8	-13 ± 8†
Naproxen	127 ± 7	-49 ± 7*	-14 ± 8	1 ± 8	2 ± 7	21 ± 8	-2 ± 9	-2 ± 8	0 ± 7	14 ± 9

* Significantly different from Baseline; p≤ 0.05.
† Significantly different from naproxen; p≤ 0.05.

Renal Effects in Patients with Chronic Renal Insufficiency: Study 036

In a multi-center, double-blind, randomized, placebo-controlled study, 71 patients with stable chronic renal insufficiency received either celecoxib 200 mg BID, naproxen 500 mg BID or placebo for seven days. Renal insufficiency was defined as a diminished GFR of (b)(4) and an elevated but stable serum creatinine level (b)(4) with no change in this value >1 mg/dL in the previous six months.

GFR was unchanged with celecoxib 200 mg BID when compared to naproxen 500 mg BID treatment or to placebo treatment (Table 85). Similarly no significant treatment effects were observed with naproxen 500 mg BID compared to placebo treatment. On Day 7, there was a trend for GFR to decline with time in all treatment groups including placebo and a statistically significant decrease was evident at the 1-2 hour timepoint for naproxen and the 2-3 hour postdose timepoint for celecoxib. Fractional sodium excretion with celecoxib 200 mg BID or naproxen 500 mg BID treatment was unchanged when compared to placebo treatment and no differences between celecoxib 200 mg BID and naproxen 500 mg BID treatment were evident. However, within-treatment group comparisons showed that fractional sodium excretion was significantly reduced with celecoxib 200 mg BID and naproxen 500 mg BID at most time points postdose on Day 1 from predose values. No treatment-related effects were evident on Day 7. Plasma renin activity (PRA) was not affected by celecoxib 200 mg BID or naproxen 500 mg BID treatment when compared to placebo treatment on Day 1 or on Day 7.

Table 85. GFR and Fractional Sodium Excretion in Patients with Chronic Renal Insufficiency: Study 036

	GFR (mL/min/1.73m²)			Fractional Sodium Excretion (%)		
Assessment(a)	Placebo (N=19)	Celecoxib 200 mg BID (N=19)	Naproxen 500 mg BID (N=22)	Placebo (N=19)	Celecoxib 200 mg BID (N=19)	Naproxen 500 mg BID (N=22)
Day 1						
Pre-dose	31.8 ± 2.0	31.5 ± 3.7	36.9 ± 2.6	2.6 ± 0.7	2.9 ± 0.6	3.4 ± 1.0
Postdose (Change from Baseline)						
0-1 hr	2.3 ± 2.6	2.6 ± 2.7	-1.5 ± 2.7	-0.5 ± 0.4	-0.9 ± 0.4*	-0.6 ± 0.2*
1-2 hr	1.7 ± 2.5	-2.2 ± 2.2	-3.9 ± 2.1	-0.8 ± 0.6	-1.0 ± 0.5*	-1.5 ± 0.4*
2-3 hr	-1.8 ± 2.0	-1.7 ± 2.7	-0.5 ± 2.5	-0.9 ± 0.7	-1.2 ± 0.4*	-1.9 ± 0.6*
Day 7						
Pre-dose	34.4 ± 3.7	35.4 ± 3.2	37.1 ± 3.4	2.1 ± 0.5	3.6 ± 0.8	3.4 ± 0.9
Postdose (Change from Baseline)						
0-1 hr	-2.1 ± 3.0	-4.0 ± 2.6	-5.3 ± 3.1	-0.3 ± 0.5	0.1 ± 0.5	0.6 ± 0.4
1-2 hr	-3.2 ± 3.1	-4.2 ± 3.7	-6.7 ± 2.7*	-0.3 ± 0.5	0.1 ± 0.8	0.3 ± 0.6
2-3 hr	-1.2 ± 3.9	-5.1 ± 2.4*	-4.2 ± 3.4	-0.5 ± 0.5	-1.0 ± 0.6	-0.5 ± 0.6

Values are expressed as mean ± SE
* Significantly different from the pre-dose level within treatment group; $p \leq 0.05$.
(a) If GFR could not be calculated or exceeded 175 ml/min/1.73m², the patient was excluded from the modified ITT cohort.

Renal Effects in Sodium-Depleted Young Healthy Subjects: Study 033

Study 033 was a single-center, double-blind, randomized, placebo-controlled, outpatient study comparing the renal effects of celecoxib to naproxen in sodium-depleted subjects.

Forty-one healthy young male subjects received celecoxib 200 mg BID, celecoxib 400 mg BID, naproxen 500 mg BID or placebo for seven days. Lack of adequate stimulation of the renin-angiotensin system in this study limited the activation of renal prostaglandin synthesis as a counterregulatory mechanism and resulted in the apparent inability to detect prostaglandin-mediated effects on renal function with dosing of naproxen. Additionally, large within-subject variability for GFR determinations obscured any treatment-related effects that may have taken place and precluded any meaningful analysis.

6.3.10.3.7 Summary and Conclusions

The incidence of renal adverse events with celecoxib was low and only marginally greater than placebo although this difference did achieve statistical significance. The most common adverse event that occurred with celecoxib treatment was peripheral edema. The incidence of peripheral edema and all other renal adverse events with celecoxib was similar to NSAIDs. Peripheral edema in celecoxib-treated patients was not associated with significant increases in body weight or blood pressure. Celecoxib was not associated with measurable changes in GFR in subgroups that are considered to be susceptible to the renal hemodynamic effects of NSAIDs. However, transient reductions in urinary sodium excretion were evident with celecoxib. The magnitude of this acute antinatriuretic effect was similar to that observed with NSAIDs. The clinical significance of the observations described above are uncertain and the evidence is inconclusive to determine whether celecoxib offers any renal safety benefit when compared to NSAID therapy. The available evidence suggests that the renal effects of celecoxib may be similar to NSAIDs.

6.3.10.4 Hematologic Effects

6.3.10.4.1 Adverse Events

Table 86 shows the incidences of adverse events relevant to bleeding, hemorrhagic or clotting abnormalities in the North American Controlled Arthritis Trials that occurred with incidence of 0.5% or greater in any treatment group. For celecoxib, the overall incidence of any adverse event related to bleeding varied (b)(4) Although the highest overall celecoxib incidence occurred for the 400 mg BID dosage, there was no apparent dose-response effect. The incidence for NSAIDs was the highest at 3.8%, mostly resulting from the incidences of anemia and ecchymosis.

Table 86. Bleeding-Related Adverse Events as Determined by the Investigator with an Incidence ≥0.5% in Any Treatment Group: North American Controlled Arthritis Trials

		Celecoxib					
Adverse Event	**Placebo**	**50 mg BID**	**100 mg BID**	**200 mg QD**	**200 mg BID**	**400 mg BID**	**NSAID**
No. treated	1864	690	1779	453	1914	615	2098
Any bleeding event	1.6	2.2	1.6	1.3	2.2	2.3	3.8
Vaginal hemorrhage	<0.1	0.2	<0.1	0.7	0.0	0.2	0.1
Anemia	0.4	0.6	0.3	0.4	0.7	0.8	1.6
Ecchymosis	0.3	0.6	0.2	0.2	0.6	0.5	1.0

All numbers are percentages of patients unless otherwise specified.

Table 87 shows the statistical comparisons between recommended therapeutic doses of celecoxib and either placebo or NSAIDs for adverse events occurring in 0.5% or more of patients. No differences between celecoxib and placebo were statistically significant. However, the incidences of anemia, ecchymosis, and any bleeding-related event overall were statistically significantly higher for NSAIDs than for celecoxib.

Table 87. Analysis of Bleeding-Related Adverse Events between Celecoxib and Placebo or NSAIDs

Adverse Event	**Celecoxib***	**Placebo**	**p Value**	**Celecoxib***	**NSAIDs**	**p Value**
No. treated	3512	1864	-	2890	2098	-
Any bleeding event	1.7	1.6	-	1.9	3.8	<0.001
Vaginal Hemorrhage	0.1	<0.1	-	<0.1	0.1	-
Anemia	0.5	0.4	-	0.5	1.6	<0.001
Ecchymosis	0.3	0.3	-	0.4	1.0	0.015

Data are expressed in percentages of patients (except for p values).

6.3.10.4.2 Adverse Events Causing Withdrawal

Six patients receiving NSAIDs withdrew due to anemia as compared with two patients receiving therapeutic doses of celecoxib and four patients overall. No placebo-treated patients withdrew for anemia. One celecoxib-treated patient and one NSAID-treated patient withdrew for ecchymosis.

6.3.10.4.3 Serious Adverse Events

In the North American Controlled Arthritis Trials, no predominance of any single treatment group was suggested by analysis of serious adverse events possibly related to bleeding- or clotting-related disorders. The events analyzed were compiled from several body systems, including "platelet, bleeding and clotting disorders," "red blood cell

disorders," and "vascular (extracardiac) disorders." Four vascular (extracardiac) serious adverse events occurred in patients receiving celecoxib (0.4 events/100 patient-years), in four patients receiving NSAIDs (0.7 events/100 patient-years), and in two patients receiving placebo (1.0 events/100 patient-years). In addition, two patients, one taking celecoxib and the other taking an NSAID had a serious adverse event related to anemia. Finally, pulmonary embolism occurred in three NSAID-treated patients and one patient receiving celecoxib.

In the North American Long-term Open Label Arthritis Study, no single celecoxib dose level group predominated, indicating the absence of a dose response effect in the incidence of serious adverse events. Nineteen serious adverse events related to extracardiac vascular disorders occurred in patients in the North American Long-term Open Label Arthritis Study resulting in an incidence of 0.7 events per 100 patient-years of exposure.

6.3.10.4.4 Clinical Laboratory Results

Incidences of changes in clinical laboratory values in the North American 12-Week Placebo- and Active-Controlled Arthritis Trials were analyzed to assess the rate of clinically significant hematologic dysfunction (Table 88).

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Table 88. Incidence of Hematologic Laboratory Changes: North American 12-Week Placebo- and Active-Controlled Arthritis Trials

Parameter	Celecoxib 100 and 200 mg BID		Placebo		Naproxen 500 mg BID	
	No. of Patients(a)	%	No. of Patients(a)	%	No. of Patients(a)	%
Hemoglobin	2088		1009		1007	
<10 g/dL		0.4		0.3		0.5
<6 g/dL or >3 g/dL decrease		0.1		0.1		0.3
Hematocrit	2146		1045		1039	
<0.30		0.1		0.3		0.19
<0.25 or >0.10 decrease		0.1		0		0.19
RBC	1990		978		978	
<4.0 x 10^{12}/L		7.8		4.8		10.8
<3.0 x 10^{12}/L		'0		0		0
WBC	2052		1009		1014	
<4.0 x 10^{12}/L		4.9		3.9		3.3
<2.0 x 10^{12}/L		0.1		0		0
Platelets	2117		1044		1043	
<100 x 10^{9}/L		0.1		0.1		0.1
<25 x 10^{9}/L		0		0		0
Eosinophils	2176		1066		1061	
>0.7 x 10^{9}/L		0.3		0.4		0.4
>0.99 x 10^{9}/L		0.1		0.1		0.3
Neutrophils	2157		1068		1062	
<1.0 x 10^{9}/L		0.1		0.1		0
<0.5 x 10^{9}/L		0		0.1		0
PT	2034		1000		993	
>18 sec		0.7		0.4		0.8
>36 sec		0.1		0.2		0.1
PTT	1944		967		957	
>40 sec		4.1		4.1		3.6
>59 sec		0.9		0.5		0.7

a) No. of patients with normal values at Baseline

6.3.10.4.5 Summary and Conclusions

Celecoxib has no clinically important hematologic effects as assessed by adverse events and clinical laboratory parameters.

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7.0 BENEFIT/RISK RELATIONSHIP

7.1 Summary of the Benefits of Celecoxib

- Celecoxib is efficacious in the treatment of the signs and symptoms of OA, RA and in the management of pain.
- Celecoxib has been well tolerated by all populations studied, which are representative of the intended patient population. There is no evidence of dose-related increases in the incidence or type of adverse events. Over 500 arthritis patients have been treated with 2-4 times the full therapeutic dose for more than 3 months.
- The incidence of gastroduodenal ulcers that occurred with celecoxib both at therapeutic doses and 2-4 times the therapeutic dose, was significantly less than with NSAIDs and similar to placebo.
- The annual incidence of clinically significant UGI complications with celecoxib was only 0.20%. This incidence was significantly less than the 1.68% observed with NSAIDs and similar to that of placebo.
- Celecoxib did not affect platelet function at doses up to12 times higher than the therapeutic dose.
- Celecoxib does not have clinically important interactions with other drugs including methotrexate, warfarin, lithium, glyburide, tolbutamide, or phenytoin.

7.2 Summary of Risks of Celecoxib

- The novel COX-2 selective mechanism of action of celecoxib may result in unexpected toxicities.
- No prospective studies have been conducted in patients with advanced renal disease, congestive heart failure or liver dysfunction.
- The incidence of UGI complications with celecoxib (0.20%) was too low to identify patient populations at risk. UGI complications may occur in patients on celecoxib who have independent causal factors for the development of ulcer such as concurrent use of aspirin or *H. pylori* infection.
- The pharmacological activity of celecoxib to reduce pain and inflammation may mask and diminish the utility of these diagnostic signs in detecting infections.
- Celecoxib may be associated with reactions or exacerbations in patients with a history of sulfa allergy or NSAID-induced hypersensitivity reactions.

- Celecoxib has not been evaluated in patients with the aspirin triad (nasal polyps, rhinitis and asthma), or in patients who exhibit hypersensitivity reactions after taking aspirin or NSAIDs.
- Studies of celecoxib excretion in human milk have not been conducted but celecoxib has been shown to be excreted in rat milk.
- The effects of celecoxib on growth and development in pediatric patients are not known.

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8.0 CONCLUSIONS OF THE CELECOXIB CLINICAL PROGRAM

Based on the results of clinical trials, it is concluded that celecoxib is efficacious in the treatment of the signs and symptoms of OA and RA and in the management of pain. The recommended therapeutic dose for OA is 200 mg per day administered as a single dose or as divided doses and the recommended therapeutic dose for RA is 100 mg or 200 mg BID. For alleviating acute pain, doses of 100 mg or 200 mg administered as needed every 4-6 hours up to a maximum daily dose of 400 mg are therapeutic.

Celecoxib has a wide therapeutic index and does not have the UGI toxicity or inhibitory platelet effects associated with COX-1 inhibition. The incidence of gastroduodenal ulceration and clinically significant UGI events in celecoxib treated patients at 2-4 times the full therapeutic dose was similar to placebo and significantly lower than with NSAIDs. At 6-12 times the therapeutic dose, celecoxib had no effect on platelet function.

Overall, celecoxib was well tolerated. GI symptoms (dyspepsia, nausea, abdominal pain) were more common in patients receiving celecoxib than in patients on placebo but significantly less than in patients receiving NSAIDs. Renal-related adverse events such as peripheral edema, were uncommon but more frequent than with placebo and similar to NSAIDs. Celecoxib had no apparent effects on vital signs and no adverse hematologic or hepatic effects.

As a specific COX-2 inhibitor, celecoxib has anti-inflammatory and analgesic properties without many of the mechanism-based, potentially serious adverse effects of non-selective COX inhibitors, NSAIDs. As such, this novel compound is an important contribution to the medical armamentarium for treating arthritis and pain.

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LABELING

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Arthritis Advisory Committee

Food and Drug Administration
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Agenda and Questions